

WHAT IS CLAIMED IS:

1 1. An immunoglobulin molecule or fragment thereof comprising a region
2 where amino acid residues corresponding to at least a portion of a complementarity
3 determining region (CDR) are replaced with a peptide mimetic selected from the group
4 consisting of an EPO mimetic and a TPO mimetic.

1 2. An immunoglobulin molecule or fragment thereof according to claim 1
2 further comprising at least one flanking sequence including at least one amino acid
3 covalently linked to at least one end of the peptide mimetic.

1 3. An immunoglobulin molecule or fragment thereof according to claim 2
2 wherein the at least one flanking sequence includes a flanking sequence having a
3 proline that is covalently linked to the peptide mimetic.

1 4. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein at least two complementarity determining regions (CDRs) are replaced with
3 the peptide mimetic.

1 5. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the immunoglobulin molecule fragment is selected from the group consisting
3 of Fab fragment, F(ab')₂ fragment and ScFv fragment.

1 6. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the immunoglobulin molecule is a full IgG molecule.

1 7. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the CDR is located on a light chain.

1 8. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the CDR is located on a heavy chain.

1 9. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the CDR is selected from the group consisting of a CDR3 of a heavy chain
3 and a CDR2 of a light chain.

1 10. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the CDR is selected from the group consisting of CDR3 of a heavy chain and
3 CDR2 of a heavy chain.

1 11. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the CDR is selected from the group consisting of CDR3 of a heavy chain and
3 CDR1 of a light chain.

1 12. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein amino acid residues corresponding to a portion of more than one CDR are
3 replaced.

1 13. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the CDR3 regions of a heavy chain and a light chain are replaced with the
3 peptide mimetic.

1 14. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the CDR includes both CDR2 and CDR3.

1 15. An immunoglobulin molecule or fragment thereof according to claim 14
2 wherein the CDR is located in a heavy chain.

1 16. An immunoglobulin molecule or fragment thereof according to claim 14
2 wherein the CDR is located in a light chain.

1 17. An immunoglobulin or fragment thereof according to claim 1 wherein the
2 EPO mimetic corresponds to the sequence set forth in SEQ. ID. NO. 3.

1 18. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the TPO mimetic corresponds to the sequence set forth in SEQ. ID. NO. 1.

1 19. An immunoglobulin molecule or fragment thereof according to claim 3
2 wherein the CDR is replaced with a peptide having a sequence including that set forth
3 in SEQ. ID. NO. 2.

1 20. An immunoglobulin molecule or fragment thereof according to claim 2
2 wherein the CDR is replaced with a peptide having a sequence selected from the
3 group consisting of SEQ. ID. NO. 25, SEQ. ID. NO. 27, SEQ. ID. NO. 29, SEQ. ID.
4 NO. 31, SEQ. ID. NO. 33, SEQ. ID. NO. 35, SEQ. ID. NO. 37, SEQ. ID. NO. 39, SEQ.
5 ID. NO. 41, SEQ. ID. NO. 43, SEQ. ID. NO. 45, SEQ. ID. NO. 47, and SEQ. ID. NO.
6 49.

1 21. An immunoglobulin molecule or fragment thereof according to claim 2
2 wherein the CDR is replaced with a peptide having a sequence selected from the
3 group consisting of SEQ. ID. NO. 31, SEQ. ID. NO. 35, SEQ. ID. NO. 37, SEQ. ID.
4 NO. 39, SEQ. ID. NO. 41, SEQ. ID. NO. 43, SEQ. ID. NO. 45, and SEQ. ID. NO. 49.

1 22. An immunoglobulin molecule or fragment thereof according to claim 1
2 wherein the immunoglobulin molecule or fragment thereof is human.

1 23. An immunoglobulin molecule or fragment thereof according to claim 22
2 wherein the immunoglobulin molecule or fragment thereof is anti-tetanus toxoid.

1 24. Nucleic acid encoding an immunoglobulin molecule or fragment thereof
2 according to claim 1.

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1 25. Nucleic acid encoding an immunoglobulin molecule or fragment thereof
2 according to claim 2.

1 26. Nucleic acid encoding an immunoglobulin molecule or fragment thereof
2 according to claim 21.

1 27. An expression vector comprising nucleic acid according to claim 24.

1 28. An expression vector comprising nucleic acid according to claim 25.

1 29. An expression vector comprising nucleic acid according to claim 26.

1 30. A host cell transformed with an expression vector according to claim 27.

1 31. A host cell transformed with an expression vector according to claim 28.

1 32. A host cell transformed with an expression vector according to claim 29.

1 33. A method of producing an immunoglobulin molecule or fragment thereof
2 comprising culturing a host cell according to claim 30 under conditions suitable for
3 expression of the immunoglobulin or fragment thereof.

1 34. A method of producing an immunoglobulin molecule or fragment thereof
2 comprising culturing a host cell according to claim 31 under conditions suitable for
3 expression of the immunoglobulin or fragment thereof.

1 35. A method of producing an immunoglobulin molecule or fragment thereof
2 comprising culturing a host cell according to claim 32 under conditions suitable for
3 expression of the immunoglobulin or fragment thereof.

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1 36. A composition comprising an immunoglobulin or fragment thereof
2 according to claim 1 and a pharmaceutically acceptable carrier.

1 37. A method of engineering an immunoglobulin molecule or fragment
2 thereof to exhibit an activity of a biologically active peptide comprising:
3 providing nucleic acid encoding an immunoglobulin molecule or a
4 fragment thereof;
5 replacing at least a portion of at least one CDR encoding region with
6 nucleic acid encoding a biologically active peptide selected from the group consisting
7 of TPO mimetic and EPO mimetic to form a biologically active peptide substituted
8 nucleic acid construct; and
9 expressing the peptide encoded by the nucleic acid construct along with
10 an antibody chain selected from the group consisting of heavy chain and light chain, in
11 a suitable host cell such that a heterodimer is formed.

1 38. A method according to claim 37 wherein the biologically active peptide
2 includes a proline covalently attached to its carboxy terminus.

1 39. A method according to claim 38 wherein the biologically active peptide is
2 selected from the group consisting of SEQ. ID. NO: 31, SEQ. ID. NO: 35, SEQ. ID.
3 NO: 37, SEQ. ID. NO: 39, SEQ. ID. NO: 41, SEQ. ID. NO: 43, SEQ. ID. NO: 45, and
4 SEQ. ID. NO: 49.

1 40. A method of stimulating proliferation, differentiation, or growth of
2 promegakaryocytes or megakaryocytes, comprising contacting promegakaryocytes or
3 megakaryocytes with an effective amount of an immunoglobulin molecule or fragment
4 thereof having one or more CDR regions replaced with a TPO mimetic peptide.

1 41. A method according to claim 40 wherein platelet production is increased.

1 42. A method according to claim 40 wherein the TPO mimetic peptide is
2 selected from the group consisting of SEQ. ID. NO: 31, SEQ. ID. NO: 35, SEQ. ID.
3 NO: 37, SEQ. ID. NO: 39, SEQ. ID. NO: 41, SEQ. ID. NO: 43, SEQ. ID. NO: 45, and
4 SEQ. ID. NO: 49.

1 43. A method of increasing the production of red blood cells comprising
2 contacting hemopoietic stem cells or progenitors thereof with an effective amount of an
3 immunoglobulin molecule or fragment thereof having one or more CDR regions
4 replaced with an EPO mimetic peptide.

10006593 "120501" 1 44. An immunoglobulin molecule or fragment thereof comprising a region
2 where amino acid residues corresponding to at least a portion of a CDR are replaced
3 with a biologically active peptide flanked with a proline at the carboxy terminus of the
4 biologically active peptide.

1 45. An immunoglobulin molecule or fragment thereof according to claim 44
2 wherein at least two CDR regions are replaced with the biologically active peptide.

1 46. Nucleic acid encoding an immunoglobulin molecule or fragment thereof
2 according to claim 44.

1 47. An expression vector comprising a nucleic acid according to claim 46.

1 48. A host cell transformed with an expression vector according to claim 47.

1 49. An immunoglobulin molecule or fragment thereof comprising a region
2 where amino acid residues corresponding to at least a portion of a CDR sequence are
3 fused to a peptide mimetic selected from the group consisting of an EPO mimetic or a
4 TPO mimetic.

1 50. An immunoglobulin molecule or fragment thereof according to claim 49
2 further comprising at least one flanking sequence including at least one amino acid
3 covalently linked to at least one end of the peptide mimetic.

1 51. An immunoglobulin molecule or fragment thereof according to claim 50
2 wherein the at least one flanking sequence includes a flanking sequence having a
3 proline that is covalently linked to the carboxy terminus of the peptide mimetic.

1 52. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein at least two CDRs are fused to respective peptide mimetics.

1 53. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the immunoglobulin molecule fragment is selected from the group consisting
3 of Fab fragment, F(ab')₂ fragment and ScFv fragment.

1 54. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the immunoglobulin molecule is a full IgG molecule.

1 55. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is located on a light chain.

1 56. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is located on a heavy chain.

1 57. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is selected from the group consisting of CDR2 of a heavy chain and
3 CDR2 of a light chain.

1 58. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is selected from the group consisting of CDR1 of a heavy chain and
3 CDR1 of a light chain.

1 59. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein amino acid residues corresponding to a portion of more than one CDR are
3 replaced.

1 60. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR is selected from the group consisting of a CDR3 of a heavy chain
3 and a CDR3 of a light chain.

1 61. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR3 regions of a heavy chain and a light chain are fused with the
3 peptide mimetic.

1 62. An immunoglobulin molecule or fragment thereof according to claim 49
2 wherein the CDR includes both CDR2 and CDR3.

1 63. An immunoglobulin molecule or fragment thereof according to claim 62
2 wherein the CDR is located in a heavy chain.

1 64. An immunoglobulin molecule or fragment thereof according to claim 62
2 wherein the CDR is located in a light chain.

1 65. Nucleic acid encoding an immunoglobulin or fragment thereof according
2 to claim 49.

1 66. Nucleic acid encoding an immunoglobulin or fragment thereof according
2 to claim 50.

1 67. An expression vector comprising nucleic acid according to claim 65.

1 68. An expression vector comprising nucleic acid according to claim 66.

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1 69. A host cell transformed with an expression vector according to claim 67.

1 70. A host cell transformed with an expression vector according to claim 68.

1 71. A method of producing an immunoglobulin molecule or a fragment
2 thereof comprising culturing a host cell according to claim 69 under conditions suitable
3 for expression of the immunoglobulin or fragment thereof.

1 72. A method of producing an immunoglobulin molecule or a fragment
2 thereof comprising culturing a host cell according to claim 70 under conditions suitable
3 for expression of the immunoglobulin or fragment thereof.

1 73. A composition comprising an immunoglobulin or fragment thereof
2 according to claim 49 and a pharmaceutically acceptable carrier.

1 74. A method of engineering an immunoglobulin molecule or fragment
2 thereof to exhibit an activity of a biologically active peptide comprising:
3 providing nucleic acid encoding an immunoglobulin molecule or a
4 fragment thereof;
5 fusing at least a portion of at least one CDR encoding region with a
6 biologically active peptide selected from the group consisting of TPO mimetic and EPO
7 mimetic to form a biologically active peptide substituted nucleic acid construct; and
8 expressing the peptide encoded by the nucleic acid construct along with
9 an antibody chain selected from the group consisting of heavy chain and light chain, in
10 a suitable host cell such that a heterodimer is formed.

1 75. A method according to claim 74 wherein the biologically active peptide
2 includes a proline covalently attached to its carboxy terminus.

1 76. A method of stimulating proliferation, differentiation or growth of
2 promegakaryocytes or megakaryocytes comprising contacting

3 promegakaryocytes or megakaryocytes with an effective amount of an
4 immunoglobulin molecule or fragment thereof having one or more CDRs fused to
5 a TPO mimetic peptide.

1 77. A method of increasing the production of red blood cells comprising
2 contacting hemopoietic stem cells or progenitors thereof with an effective amount of an
3 immunoglobulin molecule or fragment thereof having one or more CDR regions are
4 fused to an EPO mimetic peptide.

1 78. An immunoglobulin molecule or fragment thereof comprising a region
2 where amino acid residues corresponding to at least a portion of a CDR are fused with
3 a biologically active peptide flanked with a proline at the carboxy terminus of the
4 biologically active peptide.

1 79. An immunoglobulin molecule or fragment thereof according to claim 78
2 wherein at least two CDR regions are replaced with the biologically active peptide.

1 80. Nucleic acid encoding an immunoglobulin molecule or fragment thereof
2 according to claim 78.

1 81. An expression vector comprising a nucleic acid according to claim 80.

1 82. A host cell transformed with an expression vector according to claim 81.

1 83. A library containing varied immunoglobulin molecules or fragments
2 thereof wherein amino acid residues corresponding to at least a portion of at least one
3 CDR are replaced with a peptide mimetic selected from the group consisting of an
4 EPO mimetic and a TPO mimetic, the peptide mimetic having at least one flanking
5 sequence which has been randomized to generate immunoglobulin molecules or
6 fragments thereof having variable amino acid sequences.

1 84. A library containing varied immunoglobulin molecules or fragments
2 thereof wherein amino acid residues corresponding to at least a portion of at least one
3 CDR are fused with a peptide mimetic selected from the group consisting of an EPO
4 mimetic and a TPO mimetic, the peptide mimetic having at least one flanking
5 sequence which has been randomized to generate immunoglobulin molecules or
6 fragments thereof having variable amino acid sequences.

1 85. An immunoglobulin molecule or fragment thereof according to claim 44
2 wherein the biologically active peptide is flanked at both its carboxy terminus and its
3 amino terminus.

with a
proline?

1 86. An immunoglobulin molecule or fragment thereof according to claim 85
2 wherein the biologically active peptide is flanked at its carboxy terminus with an amino
3 acid sequence selected from the group consisting of proline-valine, proline-aspartic
4 acid, proline-isoleucine, serine-asparagine, serine-lysine, serine-glycine, serine-
5 arginine, leucine-histidine, leucine-glutamic acid, leucine-alanine, leucine-
6 phenylalanine, valine-glutamine, valine-serine, valine-alanine, valine-asparagine,
7 isoleucine-serine, isoleucine-tyrosine, asparagine-proline, asparagine-serine, asparagine-
8 tryptophan, asparagine-valine, phenylalanine-valine, threonine-serine, methionine-
9 alanine, arginine-serine, arginine-glycine, arginine-threonine, arginine-leucine,
10 arginine-valine, tryptophan-arginine, tryptophan-tryptophan, alanine-arginine, aspartic
11 acid-valine, glycine-tyrosine, glutamine-arginine, and glycine-lysine.

1 87. An immunoglobulin molecule or fragment thereof according to claim 44
2 wherein the biologically active peptide is flanked at its carboxy terminus with an amino
3 acid sequence selected from the group consisting of proline-valine, proline-aspartic
4 acid, proline-isoleucine, serine-asparagine, serine-lysine, serine-glycine, serine-
5 arginine, leucine-histidine, leucine-glutamic acid, leucine-alanine, leucine-
6 phenylalanine, valine-glutamine, valine-serine, valine-alanine, valine-asparagine,
7 isoleucine-serine, isoleucine-tyrosine, asparagine-proline, asparagine-serine, asparagine-
8 tryptophan, asparagine-valine, phenylalanine-valine, threonine-serine, methionine-

9 alanine, arginine-serine, arginine-glycine, arginine-threonine, arginine-leucine,
10 arginine-valine, tryptophan-arginine, tryptophan-tryptophan, alanine-arginine, aspartic
11 acid-valine, glycine-tyrosine, glutamine-arginine, and glycine-lysine.

1 88. An immunoglobulin molecule or fragment thereof according to claim 44
2 wherein the biologically active peptide is flanked at its amino terminus with an amino
3 acid sequence selected from the group consisting of tryptophan-leucine, valine-valine,
4 glycine-proline, leucine-proline, leucine-tyrosine, serine-leucine, serine-isoleucine,
5 serine-proline, threonine-methionine, threonine-tyrosine, threonine-proline, glutamine-
6 threonine, glutamine-glutamic acid, glutamine-leucine, arginine-methionine, arginine-
7 asparagine, arginine-threonine, arginine-glycine, arginine-serine, lysine-glutamic acid,
8 lysine-glycine, alanine-histidine, histidine-glycine, histidine-leucine and asparagine—
9 proline.

1 89. An immunoglobulin molecule or fragment thereof according to claim 85
2 wherein the biologically active peptide is flanked at its amino terminus with an amino
3 acid sequence selected from the group consisting of tryptophan-leucine, valine-valine,
4 glycine-proline, leucine-proline, leucine-tyrosine, serine-leucine, serine-isoleucine,
5 serine-proline, threonine-methionine, threonine-tyrosine, threonine-proline, glutamine-
6 threonine, glutamine-glutamic acid, glutamine-leucine, arginine-methionine, arginine-
7 asparagine, arginine-threonine, arginine-glycine, arginine-serine, lysine-glutamic acid,
8 lysine-glycine, alanine-histidine, histidine-glycine, histidine-leucine and asparagine—
9 proline.

1 90. An immunoglobulin molecule or fragment thereof according to claim 4
2 wherein the at least two CDRs are selected from the group consisting of heavy chain
3 CDR3-heavy chain CDR2, heavy chain CDR3-light chain CDR2, heavy chain CDR2-
4 light chain CDR2, heavy chain CDR3-heavy chain CDR2-light chain CDR2 and heavy
5 chain CDR3-light chain CDR1.

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1 91. An immunoglobulin molecule or fragment thereof according to claim 4
2 wherein a heavy chain CDR3 is replaced with a peptide mimetic having SEQ ID NO.
3 40 and a light chain CDR2 is replaced with a peptide mimetic having SEQ ID NO. 61.

1 92. An immunoglobulin molecule or fragment thereof according to claim 45
2 wherein a heavy chain CDR3 is replaced with a peptide mimetic having SEQ ID NO.
3 40 and a light chain CDR2 is replaced with a peptide mimetic having SEQ ID NO. 61.

1 93. An immunoglobulin molecule or fragment thereof according to claim 52
2 wherein a heavy chain CDR3 is replaced with a peptide mimetic having SEQ ID NO.
3 40 and a light chain CDR2 is replaced with a peptide mimetic having SEQ ID NO. 61.

1 94. A method of determining whether a substance has cMpl receptor activity
2 comprising:
3 co-transfecting full length cMpl receptor with a c-Fos promoter luciferase
4 reporter construct;
5 starving the cells;
6 stimulating the cells with the substance;
7 harvesting the cells; and
8 measuring luciferase activity.

1 95. A plasmid comprising SEQ ID NO. 111.

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